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ARTICLE TYPE

Heck-Mizoroki Coupling of Vinyliodide and Applications in The Synthesis of Dienes and Trienes

Katrina S. Madden,[#] Sylvain David,[#] Jonathan P. Knowles[§] and Andrew Whiting[#]*

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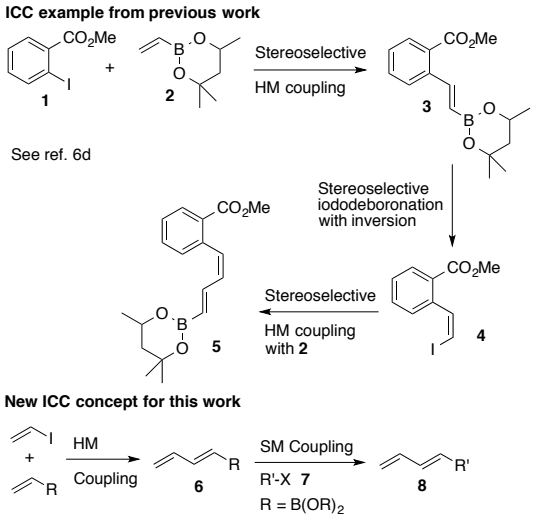
Vinyliodide reacts chemoselectively under Heck-Mizoroki conditions with terminal alkenes, including vinylboronate esters, to give dienes. The resulting dienylboronates undergo Suzuki-Miyaura coupling with aryl, heteroaryl and alkenyl halides to access dienes and trienes.

Polyenes occur widely in natural products, many with medicinal properties.[1] Whilst there are strategies by which polyenes can be synthesised,[2] new robust and reliable protocols, which deliver both high yields and stereocontrol are still required. Terminal, unsubstituted polyenes have been accessed by hydrazone formation, elimination and metal-mediated couplings,[3] however, such methods are limited by substrate scope and stereoselectivity. More recently, we applied an iterative cross-coupling (ICC) approach using vinylboronate esters as dianion equivalents through a Heck-Mizoroki (HM), iododeboronation sequence[4] in polyene synthesis.[5] Related approaches have subsequently been employed for a number of stereoselective applications.[6]



Scheme 1. An example of a highly stereoselective ICC strategy to access a triene system.[8]

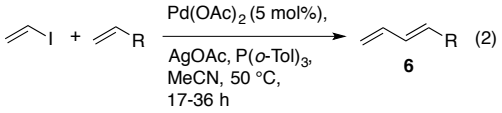
Because the Heck-Mizoroki coupling can deliver complex and stereodefined polyenes[7] and requires only one activated coupling partner (such as an alkenyl halide) [unlike the Suzuki-Miyaura (SM) coupling which requires two[7a]], it is a powerful method for application in polyene synthesis. Also, when synthesising polyenes using ICC, protecting groups are generally required that prevent direct coupling on the growing chain. For example, Scheme 1 shows an iterative Heck-Mizoroki cross-coupling, iododeboronation strategy (as used by us[8]) to interconvert a boronate ester **2** stereoselectively to an iodide **4** before the chain can be further elongated, e.g. to **5**. However, it might be possible to reduce the number of such interconversions by using a more convergent strategy. Our question was whether vinyliodide could be employed in Heck-Mizoroki couplings directly on an alkene to access a diene **6** (Scheme 1). Vinyliodide seems to have been almost completely overlooked in such couplings, except one report from Heck *et al.* in 1975[9] of a palladium-mediated reaction with methyl acrylate; the resulting diene was trapped *via* a Diels-Alder reaction without isolation.[9] We hoped that by applying the mild, chemoselective coupling conditions developed for vinylboronate Heck-Mizoroki coupling[4] would allow vinyliodide to be as used a coupling partner and enable isolation of the diene products. Herein, we report such a strategy (Scheme 1) and demonstrate some early-stage applications, particularly of using a dienylboronate for further coupling.

Preliminary examination of reaction conditions (see SI for full details of conditions screened) started with examining catalysts, bases and ligands for the reaction of vinyliodide with vinylboronate **2** (Eq. 1).

The combination of silver(I) acetate and tri-*ortho*-tolylphosphine (as optimised for previous vinylboronate-electron deficient iodoalkene reactions, as in Scheme 1[6]) gave the best conversion for Eq. 1. The catalyst loading was further tuned, with the finding that 5 mol% catalyst and shorter reaction times gave better conversions and yields (Table 1, entry 1, *i.e.* a 100% conversion of vinylboronate **2** resulted in a 73% yield of dienylboronate **6a**). Similarly, the vinylboronate pinacol ester (Table 1, entry 2) also showed good reactivity towards coupling with vinyliodide, with a conversion of 91% and an isolated yield of dienylboronate **6b** of 72%. [Note: attempts to purify these products can cause polymerisation, and hence, ca. 3 ppm of 2,6-di-*tert*-butyl-4-methyl phenol (BHT) was employed in eluents. Also, prolonged

air exposure of dienes **6a** and **b** resulted in polymerisation, hence, storage under Ar at approx. 4 °C was required with 20 ppm BHT. See ESI] These conditions were then employed in attempts to couple vinyliodide with a range of other alkenes (Eq. 2, Table 1), with differing stereoelectronic demands and functional groups.

Table 1. HM coupling using vinyliodide with different alkenes[a]



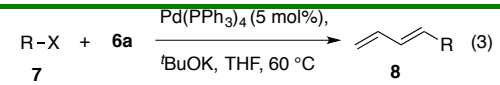
Entry	Alkene	Product (Conversion) [Isolated yield]/%[b]
1	**2**	**6a** (100) [73][c]
2	H_2C=CHBpin	**6b** R = B(Pin) (91) [72][c]
3	H_2C=$CHCO_2Me$	**6c** R = CO_2Me (42)
4	H_2C=$CHCO_2{}^tBu$	**6d** R = $CO_2{}^tBu$ (46) [28]
5	H_2C=CHCOMe	**6e** R = COMe (68)
6	H_2C=$CHSi(OMe)_3$	**6f** R = $Si(OMe)_3$ (42)
7	H_2C=$CHSi(OEt)_3$	**6g** R = $Si(OEt)_3$ (50)
8	H_2C=$CHSO_2Me$	**6h** R = SO_2Me (18)
9	H_2C=$CHPO(OMe)_2$	**6i** R = $PO(OMe)_2$ (15)
10	H_2C=$CHSnBu_3$	(0)[d]

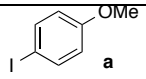
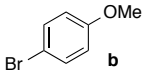
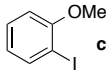
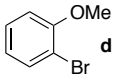
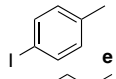
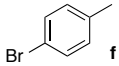
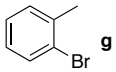
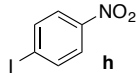
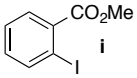
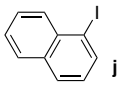
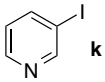
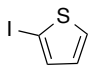
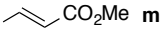
[a]Reaction conditions: See ESI. [b]Conversions determined by ^{1}H NMR. [c]1:1 ratio of vinyliodide to alkene used. [d]Stille product formed exclusively.

Under the 1:1 ratio of vinyliodide to alkene (vinylboronate) employed for the synthesis of dienylboronates **6a** and **b**, poor conversions (under 10%) were observed. Increasing to two equivalents of alkene gave greatly increased conversions, with up to 68% for methyl vinyl ketone (Table 1, entry 5). Both electronic and steric factors appeared to have an effect on the extent of reaction; the poorest conversions being those of methyl vinylsulfone and dimethyl vinylphosphonate (Table 1, entries 8 and 9). Vinyltri-n-butyltin underwent exclusive Stille coupling and no attempts were made to trap the butadiene produced. [Note: the high volatility of all the dienes **6**, along with their potential to polymerise, made them difficult to isolate in many cases and excess alkene used proved difficult to separate from dienes **6** (see Table 1)].

Following the successful isolation of dienylboronate **6a**, its utility as a four-carbon, butadienyl dianion equivalent was examined, in a manner analogous to the use of the vinylboronates, such as **2** as two-carbon, vinyl dianion equivalent building blocks (as in Scheme 1, for example).[4,10] However, dienylboronate **6a** showed no reactivity towards further Heck-Mizoroki coupling when tested against a number of aryl and alkenyl halides, including vinyl iodide. It was, however, successfully applied in Suzuki-Miyaura couplings, where it reacted with a range of aryl and alkenyl halides, including both electron-rich and electron-deficient aryl halides, heteroaryl halides and a vinyl halide (see Table 2). Despite the high reactivity of the dienylboronate **6a** (shown by high GC and ^{1}H NMR conversions), there were issues with the isolation of the products **8**, again, due to product stability. Indeed, the resulting terminally unsubstituted butadienyl analogues **8** were extremely sensitive towards polymerisation, and even more so than the starting dienylboronate **6a**. In some cases, this resulted in lower product isolated yields (after silica gel chromatography) than suggested from crude ^{1}H NMR and GC analysis [Approx. 3 ppm BHT was added to all solvents to minimise polymerisation (see ESI) which improved isolation].

Table 2. Suzuki-Miyaura coupling using dienylboronate **6a**[a]

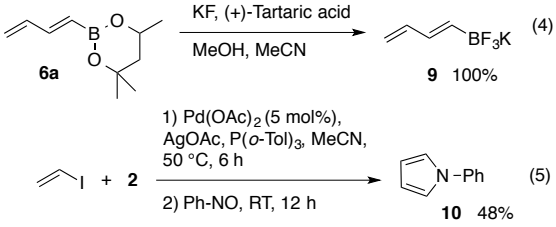


Entry	R-X **7**	Reaction time/hours	Product **8** crude (isolated) yields/%
1	 **a**	4.5	76 (69)
2	 **b**	22	32 (28)
3	 **c**	23	33 (23)
4	 **d**	25	23 (22)
5	 **e**	6	91 (89)
6	 **f**	22	74 (72)
7	 **g**	25	70 (40)
8	 **h**	6	65 (64)
9	 **i**	23	33 (24)
10	 **j**	22	73 (68)
11	 **k**	24	88 (88)
12	 **l**	23	61 (46)
13	 **m**	4	0, 58[b] (53)

[a]See ESI for reaction conditions. Yields determined by ^{1}H NMR and GC on crude product isolated after work up. [b]Ag_2O base used.

Attempts to isolate the polyenes using silver nitrate-impregnated silica[11] and other chromatographic supports did not lead to improved isolated yields. Despite this, the ability of dienylboronate **6a** to undergo coupling was demonstrated on both electron-donating and electron-withdrawing aryl iodides (Table 2, entries 1, 5, 8 and 10). In the case of *p*-iodoanisole *versus p*-bromoanisole (Table 2, entries 1 and 2), there was a drop in reactivity of the bromide compared to the iodide. However, this was not observed for the tolyl derivatives (Table 2, entries 5 and 6), where the reactivity was comparable and these derivatives showed no appreciable difference in the reactivity of the *o- versus p*-aryl halides (Table 2, entries 6 and 7), though the anisole derivatives did show a significant drop in reactivity (Table 2, entries 1 and 3). Heterocyclic compounds were also coupled (Table 2, entries 11 and 12), with 3-iodopyridine giving an isolated yield of 88%. Iodoacrylate **7m** coupled, but gave undesired side-reactions (Table 2, entry 13), however, previous work also reported competitive HI elimination, and that this could be avoided through the use of silver-salt bases.[10c] Hence, the

coupling between iodoacrylate **7m** and diene **6a** was attempted using both potassium *tert*-butoxide and silver(I) oxide. The difference between the two bases being apparent by ^{1}H NMR of the two reaction mixtures; *tert*-butoxide resulted in no triene, whereas silver(I) oxide gave 58% crude yield. In order to circumvent stability issues of diene **6a**, the corresponding trifluoroborate salt **9** was prepared[12] in quantitative yield (Eq. 4), resulting in an air stable, crystalline salt which may prove useful for Suzuki-Miyaura coupling.[13] In addition, a one-pot formation of **6a**, followed by *in situ* nitroso-Diels-Alder trapping (followed by spontaneous rearrangement and elimination)[14] provided *N*-phenyl pyrrole **10** (Eq. 5) in 48 % overall yield.



Conclusions

Vinyliodide can be employed in Heck-Mizoroki couplings to derive dienes. Vinylboronates are especially effectively giving dienylboronate **6a** which can be applied for the synthesis of terminally unsubstituted dienes and trienes. Hence, this type of ICC strategy provides an alternative to those currently used and delivers dienes and trienes in an efficient, stereoselective, atom economic manner. The facile formation of boronates **6a/b** from (Table 1) using only 1 equivalent of alkene coupling partner contrasts with most alkenes which required 2 equivalents of alkene, yet still delivered variable conversions (despite many being considered good coupling partners). This clearly has mechanistic implications which are not clear at this point. However, we speculate that under the ambient Heck-Mizoroki coupling conditions necessary, the boronate group may coordinate (e.g. to an acetoxy ligand on palladium), resulting in kinetic assistance for the HM reaction. Previous kinetic studies[7d] on vinylboronate coupling did show that the rate determining step in such reactions was not oxidative addition, rather being either ligand exchange (e.g. acetate for iodide) or carbometallation. If acetate were involved as a palladium ligand, such chelational assistance could intervene in these boronate systems, but would be absent in all the others examined, except potentially the vinyl siloxanes. Interestingly, the corresponding MIDA-vinylboronate[6f] was unreactive under the coupling conditions, potentially supporting this hypothesis and the need for an empty sp^2-hybridised orbital on boron. Further studies are underway.

Notes and references

[#]*Department of Chemistry, Durham University, South Road, Durham, DH1 3LE, UK. Email andy.whiting@durham.ac.uk*
[§]*Department of Chemistry, University of Bristol, Cantock's Close, Bristol, Avon BS8 1TS, UK*

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Graphical abstract

Heck-Mizoroki Coupling of Vinyliodide and Applications in The Synthesis of Dienes and Trienes

Katrina S. Madden, Sylvain David, Jonathan P. Knowles and Andrew Whiting*

Vinyliodide reacts chemoselectively under Heck-Mizoroki conditions with terminal alkenes to give diene products, including vinyl boronate esters, and the resulting dienylboronate undergoes Suzuki-Miyaura coupling with aryl, heteroaryl and alkenyl halides to access dienes and trienes.